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Novel indium-mediated ternary reactions between indole-3-carboxaldehydes–allyl bromide–enamines: facile synthesis of bisindolyl- and indolyl-heterocyclic alkanes

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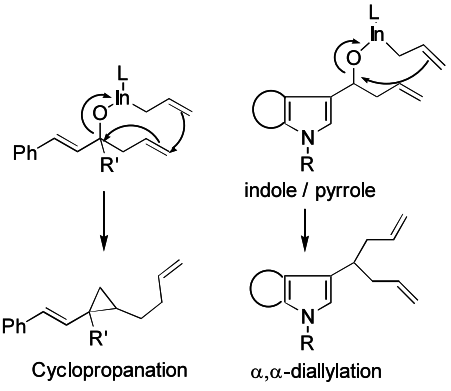
Abstract—Indole-3-carboxaldehydes undergo indium-mediated ternary reactions with allyl bromide and indoles to provide symmetrical and unsymmetrical bisindolyl alkanes and with other heterocyclic enamines viz. pyrrole, pyrazole, 6-aminouracil and imidazole to provide indolyl-heterocyclic alkanes in excellent yields. The reactions with substituted allyl bromides proceed with greater ease.

Bisindolyl alkanes and their derivatives constitute an important group of bioactive metabolites of terrestrial and marine origin.[1] Symmetrical bisindolylalkanes can be easily synthesized by Lewis- or protic acid-catalysed indole–aldehyde condensation reactions[2] but functionalised and unsymmetrical bisindolylalkane derivatives need more rigorous procedures.[3]

In recent years, the addition of allyl indium reagents to carbonyl compounds in an aqueous medium has emerged as one of the synthetically most useful methods for carbon–carbon bond formation.[4] Generally in indium-mediated allylation, the homoallylic indium alkoxide intermediate on hydrolysis yields a homoallylic alcohol as the [1,2]-addition product. In some isolated cases of α,β-unsaturated carbonyl compounds,[5] the homoallylic indium alkoxide intermediates undergo allyl anion induced deoxygenative carbon–carbon bond formation to provide cyclopropyl[6] or α,α-diallyl derivatives[7] (Scheme 1). In both cases the same allylic anion adds on to give the final product.



Scheme 1.

We envisaged that if at the intermediate homoallylic indium alkoxide stage, an external nucleophile is present, it may undergo deoxygenative carbon–carbon bond formation at the C-OIn carbon to provide a new entity with the aldehyde–allyl bromide–nucleophile as constituents. Here, we report that stirring indole-3-carboxaldehydes, allyl bromide and a heterocyclic enamine in THF–H_2O containing a suspension of indium metal provides symmetrical and unsymmetrical bisindolyl alkanes and indolyl-heterocyclic alkanes in excellent yields.

A solution of 1-benzylindole-3-carboxaldehyde **1a**, *N*-methylindole and allyl bromide (1:1:1) in THF–H_2O (2:1) containing a fine suspension of indium metal (0.7 equiv.) was stirred at 30±1°C for 2–3 h (Scheme 2).[8] The reaction mixture after aqueous work-up gave **3a** (92%), M^+ m/z 390. In its ^1H NMR spectrum, the presence of two triplets at δ 2.98 (2H) and 4.63 (1H) due to the methylene and methine protons along with the *N*-Me (δ 3.72) and *N*-CH_2 (δ 5.27) signals of the two indole units clearly showed the presence of all three components. Therefore, the reaction of **1a**, *N*-methyl indole and allyl bromide provides the unsymmetrical bis(3,3′-indolyl)methane derivative **3a**. A similar reac-

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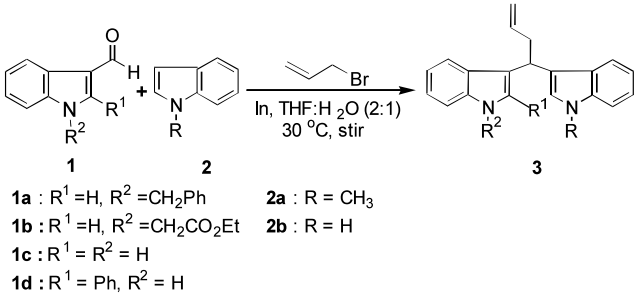
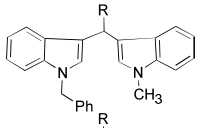
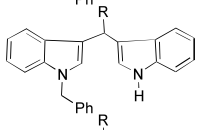
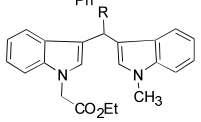
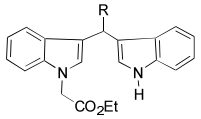
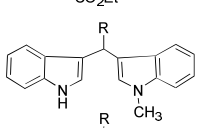
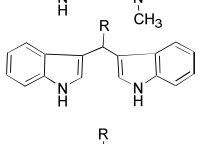
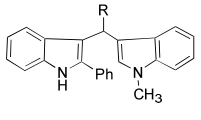
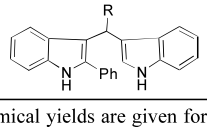


Scheme 2.

Table 1. Synthesis of symmetrical and unsymmetrical bis(indolyl)alkanes

no	indole	2a / 2b	product [a]		yield[b]
1	**1a**			**3a**	92
2	**1a**			**3b**	93
3	**1b**			**3c**	93
4	**1b**			**3d**	96
5	**1c**			**3e**	92
6	**1c**			**3f**	89
7	**1d**			**3g**	91
8	**1d**			**3h**	94

[a] R = -$CH_2CH=CH_2$, [b] % Chemical yields are given for isolated products after chromatographic purification.

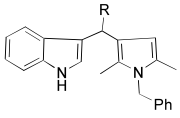
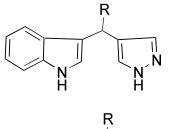
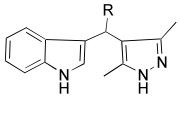
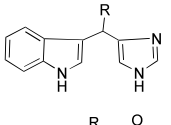
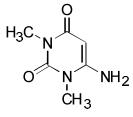
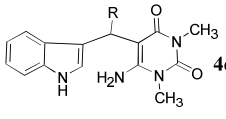
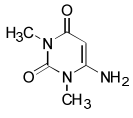
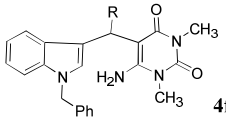
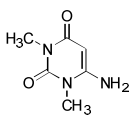
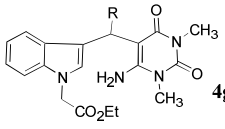
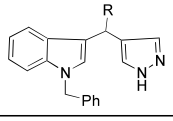
tion with indole provides the unsymmetrical bis(indolyl)alkane **3b** (Table 1, entry 2).

Indole-3-carboxaldehyde **1c**, which does not often give condensation or addition reactions of the aldehyde group,[9] on reaction with indole and allyl bromide provides the symmetrical indolyl alkane **3f** (Table 1, entry 6). Similarly, 2-phenylindole-3-carboxaldehyde **1d** with allyl bromide and indole/methyl indole provides the unsymmetrical bis(indolyl)alkanes **3g** and **3h**. Therefore, indole-3-carboxaldehydes irrespective of the substituents at *N*-1 and *C*-2 undergo facile ternary reactions to provide symmetrical and unsymmetrical bis(indolyl)alkanes **3a**–**h**.

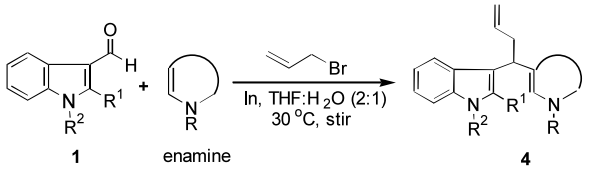
In order to broaden the scope of this ternary reaction, the reactions of indole-3-carboxaldehydes and allyl bromide with other heterocyclic enamines have been performed. (Table 2) (Scheme 3). 1-Benzyl-2,5-dimethylpyrrole, 3,5-dimethylpyrazole, pyrazole, imidazole and 6-aminouracil derivatives undergo facile ternary reactions with indole-3-carboxaldehydes and allyl bromide to provide the respective indolyl–heterocyclic alkane derivatives **4a**–**h**. The diallylated product of indole-3-carboxaldehyde was not isolated in any of these reactions.

Also, substituents on the allyl bromide do not affect these ternary reactions but due to the generation of two chiral centres result in mixtures of diastereomers (Table 3). In each case allylation proceeds with complete regioselectivity to provide only the γ-addition product.

Table 2. Synthesis of indolyl (heterocyclic) alkanes (**4**)

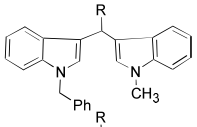
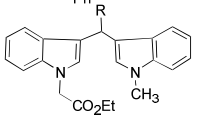
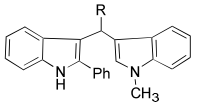
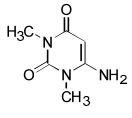
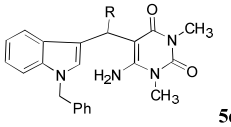
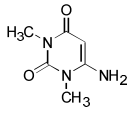
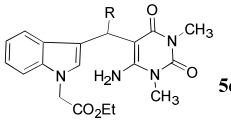
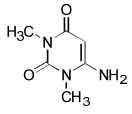
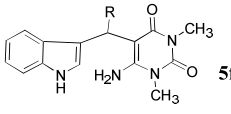
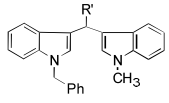
no	indole	enamine	product [a]		yield[b]
1	**1c**			**4a**	93
2	**1c**			**4b**	94
3	**1c**			**4c**	89
4	**1c**			**4d**	91
5	**1c**			**4e**	92
6	**1c**			**4f**	94
7	**1b**			**4g**	92
8	**1a**			**4h**	88

[a] R = -$CH_2CH=CH_2$, [b] % Chemical yields are given for isolated products after chromatographic purification.

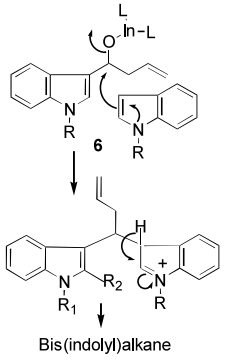


Scheme 3.

Table 3. Ternary reactions with substituted allyl bromides

no	indole	Enamine	product[a]		yield[b]
1	**1a**			**5a**	88
2	**1b**			**5b**	91
3	**1d**			**5c**	86
4	**1a**			**5d**	93
5	**1b**			**5e**	91
6	**1c**			**5f**	93
7	**1a**			**5g**	86

[a] R = -CH(CH$_3$)CH=CH$_2$ R' = CH(Ph)CH=CH$_2$, [b] % Chemical yields are given for isolated products after chromatographic purification.



Scheme 4.

The bis(indolyl) alkanes **5a–c** in their ^{1}H and ^{13}C NMR spectra do not show the presence of mixtures of diastereomers. This is probably, due to the similar electronic features of the two indole moieties resulting in the two diastereomers having similar chemical shifts. In case of indolyl-uracil akanes **5d–f**, nearly a 1:1 mixture of diastereomers was obtained as indicated by ^{1}H NMR.

These diastereomers show two signals each due to the Me, C–H and allyl CH_2 protons. The similar reaction of **1a** with cinnamyl bromide and 1-methylindole provides a 1:1 diastereomeric mixture of **5g**.

It is noteworthy that all these reactions proceed smoothly in THF–H_2O and do not require anhydrous solvents. Of particular interest is the fact that in each case only 0.7 equiv. of indium and 1 equiv. of allyl bromide is required for completion of the reaction making it a highly atom-efficient carbon–carbon bond forming process.

It is likely that indole–carboxaldehydes undergo allylation to give indium alkoxide intermediates **6** which can compete for the allylic anion and the heterocyclic enamine. However, due to the lower concentration of the allylic anion during progress of the reaction under Barbier conditions and the easy availability of the heterocyclic enamine, the reaction preferably goes with the heterocyclic enamine to provide compounds **3–5** (Scheme 4).

In summary the unique properties of indium-mediated allylations have been used to introduce new ternary reactions between indoles, allyl halides and heterocyclic enamines.

Acknowledgements

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8. *Representative procedure*: A suspension of the aldehyde (1 mmol), allyl bromide (1 mmol), heterocyclic enamine (1 mmol) and indium metal (0.7 mmol) in THF: H_2O (1:1, 5 ml) was stirred at 30°C until completion (4–6 h) of the reaction (TLC). The reaction mixture was diluted with water and extracted with dichloromethane. Evaporation of the solvent followed by purification of the crude product by silica gel column chromatography provided the pure product. All products were fully characterised by ^1H, ^{13}C NMR, IR and GCMS spectroscopy. Satisfactory elemental analysis were obtained in case of solid samples.
Spectroscopic data for ***3a***: GC–MS m/z 390 (M^+); ^1H NMR (200 MHz, $CDCl_3$): δ 2.98 (t, $J=7.6$ Hz, 2H, CH_2), 3.72 (s, 3H, CH_3), 4.63 (t, $J=7.6$ Hz, 1H, CH), 4.81–5.15 (m, 2H, $=CH_2$), 5.27 (s, 2H, NCH_2), 5.86–5.94 (m, 1H, =CH), 6.85 (s, 1H, Ind H-2), 6.97 (s, 1H, Ind H-2), 7.02–7.25 (m, 11H, ArH), 7.55–7.62 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.53, 34.03, 40.21, 49.70, 109.05, 109.57, 115.47, 118.14, 118.36, 118.69, 118.84, 119.68, 119.77, 121.22, 121.46, 126.00, 126.43, 127.08, 127.28, 127.64, 128.55, 128.66, 136.81, 137.18, 137.66, 137.91.
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